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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/812,633	03/19/2001	Thomas L. Benjamin	00742/066001	1354

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/812,633	Applicant(s) BENJAMIN ET AL.
	Examiner Janice Li	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *13-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6
4. ☐ Interview Summary (PTO-413) Paper No(s).
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Other *detailed action*

DETAILED ACTION

Election/Restrictions

Applicant's provisional election with traverse of Group I, claims 1-12, in Paper No. 10, is acknowledged. The traversal is on the ground(s) that the claims 1-12 and 13-18 are drawn to the same invention that involves identifying the presence of a proliferative disease-associated alteration in a Sal2 sequence in a mammal, that once the alteration has been identified in a Sal2 sequence, one skilled in the art would know how to assay for the presence of this alteration in a mammal using variety of assays, which assays are standard in the art. Applicants further argue that the methods are not independent and distinct as both the Sal2 nucleic acid and the protein sequence are altered in a proliferative disease-associated alteration. The arguments have been carefully considered but found not persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent methods for *detection of a protein or a nucleic acid sequence*. As such, the Invention of group II requires different reagents, method steps, protocols, and technical considerations than that of the Invention group I. In addition, although the mutation in a gene may cause the changes in the coding region of a [illegible] the instant specification teaches that the absence of $p150^{Sal2}$ expression in a majority of ovarian cancers has not lead to the loss or gross rearrangement of the *hSal2* locus, and the nucleic acid sequences in these cases are identical to published genomic sequence

of *hSal2* (1st & 2nd paragraphs in page 36). Further, different types of alterations could occur at nucleic acid and protein levels, various methods could be used for detection of each alteration, such as a short list of those methods (in claim 6) for detecting mutations in nucleic acids. The searches and considerations for groups II and I would have certain overlap, but they are not co-extensive, rejoining of the two groups would impose an undue burden to the Office. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-52 are pending, however, claims 13-52 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-12 are under current examination.

Priority

This application claims the benefit of priority from U.S. provisional application

60/216,723, filed 7/7/00.

Specification

The disclosure is objected to because of the following informalities: In the specification, the term "*mSal2*" has been used extensively, however, it is unclear what "m" stands for, "mutant", "mouse" or some other words.

The specification recites fig. 7A (line 13, page 36) and describing two panels in figure 7 (line 7, page 35), however, only figure 7 comprising one panel is present in the specification.

Appropriate clarification and correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention

is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims are directed to a method for identifying a mammal having or at increased risk of acquiring a proliferative disease, comprising the step of determining whether there is *a proliferative disease-associated alteration in a Sal2 nucleic acid* of said mammal by way of PCR, SNP, RFLP, hybridization, and mismatch detection analysis. Given the broadest reasonable interpretation, the term "a proliferative disease-associated alteration in a *Sal2* nucleic acid" encompasses numerous (a genus of) altered *Sal2* nucleic acid molecules, which are functionally associated with a proliferative disease, and which are the subjects of detection. However, the specification fails to provide an adequate disclosure for the genus of the claimed invention in terms of distinguishing characteristics of the genus.

The specification discloses the substitution of a Cys for the Ser at position 73 of Sal2 gene (a point mutation S73C) which is present in some of the ovarian tumors. However, the specification fails to provide evidence of other alterations associated with a tumor or a proliferative disease, the specification fails to disclose any abnormal pattern(s) of SNP and RELP in any proliferative-associated disease. Considering all

possible *Sal2* alterations in various tumors and other proliferative diseases, the disclosed point mutation is not a representative species of the genus. Therefore, the specification fails to provide an adequate description to teach the structures, the identifying characteristics, and the structure-function relationship of the genus of altered *Sal2* nucleic acid molecules encompassed by the claims and their disease associations, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

An adequate written description for a nucleic acid molecule requires more than a mere statement that it is part of the invention; what is required is a description of the chemical structures and physical properties of the molecule itself. It is not sufficient to define the molecules solely by its principal biological property, i.e. "a proliferative disease-associated alteration", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any molecule with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all molecules that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. what specific nucleic acid alterations to look for, which provide the means for practicing the invention. The court has made it very

clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *altered Sal2* that are associated with a proliferative disease". Therefore, only the described substitution of a Cys for the Ser at position 73 of ESQ. ID No:1 meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a point mutation S73C in *Sal2* gene, does not reasonably provide enablement for identifying a mammal having or at increased risk of acquiring a (*any*) proliferative disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature and scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention without undue experimentation.

The claims are drawn to identifying a mammal having or at increased risk of acquiring a proliferative disease by detecting alterations in *Sal2* gene. given the broadest reasonable interpretation, the claims embrace detection for a genus of altered *Sal2* nucleic acid molecules, which are associated with any and all types of proliferative diseases.

The specification teaches that human *Sal2* gene has been mapped to chromosome 14q12 and subsequently, this region of 14q is associated with a loss of homozygosity in 49% of ovarian cancers and about 25% of bladder cancers, "*these findings along with the underlying rationale of 'tumor host range' selection, suggest the possibility that sal2 may function as a tumor suppressor*" (paragraph bridging pages 34 and 35). The specification goes on to teach that out of twenty ovarian carcinomas tested, the majority (17/20) are negative for $p150^{sal2}$ (a product of Sal2 gene) expression (fig. 7), however "*no evidence of loss or gross rearrangement of the hSal2 locus was seen in any of the tumors examined*", the sequences from two tumors 327 and 523 that are negative for $p150^{sal2}$ expression, "*showed sequences identical to published genomic sequence* [of *hSal2*] (1^{st} & 2^{nd} paragraphs in page 36), while the sequences from two tumors positive for $p150^{sal2}$ expression showed a cysteine substitution for serine at position 73 of ESQ. ID No: 1. The specification goes on to teach, "*the absence of $p150^{Sal2}$ expression in a majority of ovarian cancers may reflect mechanisms other than loss of the hSal2 itself, such as silencing of expression through promoter methylation, alterations in an upstream regulatory factor, or factors leading to instability of the protein itself*" (lines 7-10, page 36), however, the specification fails to teach which one of the mechanisms is responsible for the absence of $p150^{sal2}$ expression in the instant case.

An enabled diagnostic or prognostic method should be able to provide a requisite standard or an aid for determining the nature of a disease or for distinguishing of one disease from another, in the instant case, providing a standard from the alteration(s) of *Sal2* gene for identifying a mammal having or at increased risk of acquiring a

proliferative disease. Such standard could be obtained by providing insight to various changes in *Sal2* gene and how they are associated with certain type(s) of proliferative disease(s) by way of investigation on disease heritability, gene mapping, linkage mapping, association studies in different populations, genome sequence polymorphisms, and animal models, such as those presented in USP 6,033,857 (see particularly tables 1, 3, 4-6B).

However, finding genes influencing susceptibility to complex diseases is complicated by the combinations of genes influencing a complex disease and the magnitude of environmental effects that may vary among families and populations. Taking cancer, a malignant proliferative disease, as an example, *Tavtigian et al* (USP 6,033,857) teach, "THE INVOLVEMENT OF SO MANY GENES UNDERSCORES THE COMPLEXITY OF THE GROWTH CONTROL MECHANISMS THAT OPERATE IN CELLS TO MAINTAIN THE INTEGRITY OF NORMAL TISSUE", "SO FAR, NO SINGLE GENE HAS BEEN SHOWN TO PARTICIPATE IN THE DEVELOPMENT OF ALL, OR EVEN THE MAJORITY OF HUMAN CANCERS" (column 1, lines 57-62). *Rannala* (Am J Pharmacogenom 2001;1:203-21) teaches, "GENETIC HETEROGENEITY CAN INCLUDE BOTH MULTIPLE DISEASE GENES (LOCUS HETEROGENEITY) AND MULTIPLE MUTATIONS WITHIN A DISEASE GENE (ALLELIC HETEROGENEITY)", "IT IS ENTIRELY POSSIBLE THAT MANY TRAITS ARE GREATLY AFFECTED BY GENES, BUT THAT EACH GENE INVOLVED HAS A RELATIVELY SMALL EFFECT ON ITS OWN. THUS, ALTHOUGH THE HERITABILLITY OF A TRAIT MAY BE HIGH, THE CAUSATIVE LOCI MAY BE

[illegible] left column, page 204). On the other hand, MANY [illegible]

POPULATIONS FROM WHICH INDIVIDUALS ARE SAMPLED IN STUDIES OF COMPLEX DISORDERS ARE HETEROGENEOUS; ADMIXTURE IN SUCH POPULATIONS CAN LEAD TO FALSE ASSOCIATIONS OF MARKERS WITH A DISEASE AND MAY INFLATE ESTIMATES OF HERITABILITY BECAUSE OF THE PRESENCE

OF GAMETIC PHASE DISEQUILBRIUM (left column, page 205). *Rannala* goes on to teach that "THE ULTIMATE USEFULNESS OF SUSCEPTIBILITY LOCI, ONCE IDENTIFIED, IN GENETIC COUNSELING OR IN THE DEVELOPMENT OF NEW THERAPIES IS ALSO NOT CLEAR", depending on the gene effects are additive or epistatic (2nd paragraph on right column of page 205).

In view of the state of the art and the knowledge of the skilled artisan for *Sal2* gene, *Kohlhase et al* (Mamm Genome 2000;11:64-8) teach, "NO FUNCTION IS YET KNOWN FOR *SAL2*" (abstract).

Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of genome screening for susceptibility loci in complex diseases, such as cancer or tumor, still recognized that such methods are neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed subject matter. Although the instant specification provides data from a small-scale study of ovarian cancer specimen, demonstrating that 15% (3/20) of ovarian cancer had the point mutation of S73C in *Sal2* gene, it also teaches that 85% of the ovarian cancer samples had normal *Sal2* gene. Further, the data collected only reflect a small number of certain type of proliferative disease, in a diseased population. Therefore, the specification is not enabled for the scope of the claims because it fails to teach the status of *hSal2* gene in other types of proliferative diseases and in healthy population, and it fails to establish the association between the S73C point mutation of *Sal2* gene and *any* one of the proliferative diseases.

Claims 7-12 provide a method of determining the alteration in *Sal2* gene by in site hybridization using a nucleic acid probe specific for the gene alteration. However, the alteration taught only differs in one nucleic acid base (TSGT for TACT), the specification fails to provide sufficient guidance with regard to whether such small gene alteration could be detected by *in site* hybridization method.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for obtaining a disease association of altered *Sal2* gene, in particular for any and all proliferative diseases, the lack of direction or guidance provided by the specification, and the breadth of the claims directed to the use of numerous mutations of Sal2 nucleic acids for predicting a disease susceptibility, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because the claims are incomplete. The method of claim 1 provides for identifying a mammal having an increased risk of acquiring a proliferative disease comprising determining whether there is an alteration in a Sal2 nucleic acid, however, there is no positive step to recite how the alteration is determined, and which would clearly relate back to the preamble. Method claims need

not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

These claims are vague and indefinite because claim 7 recites the limitation "said human sal2" in line 3. There is insufficient antecedent basis for this limitation in the claim.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
August 2, 2002

PRIMARY EXAMINER